Please add the following new claim:

--17. The method of Claim 6 wherein the selective inhibitor of cyclooxygenase-2 contains phenyl group with two or more substituents selected from the group consisting of hydroxy and C_{1-4}-alkoxy on the phenyl group.--

Cancel Claims 12-16 which stand withdrawn from consideration, without prejudice to pursuing them in a divisional application.

Remarks

Claims 1-11 and 17 are in the case as a result of this amendment.

Claim 1 has been amended to insert the distinguishing limitation "without administration of leukotriene B_4 receptor antagonist" to distinguish Gregory et al. U.S. Patent No. 6,172,096 which requires administration of leukotriene B_4 receptor antagonist. Basis is found in the instant application in that therapeutic results are obtained without administration of leukotriene B_4 receptor antagonist.

Claim 3 has been amended herewith to be in independent form and to delete recitation of primary biliary cirrhosis, autoimmune hepatitis and liver transplant rejection.

Claims 12-16 have been canceled.

Claim 17 has been added. Basis for new Claim 17 is found in the application as filed at page 18.

A version with markings to show changes made is attached.

Claims 7-16 have been withdrawn from further consideration as being directed to a non-elected invention. Claims 12-16 have been canceled herewith without prejudice to pursuing them

in a divisional application. Claims 7-11 remain in the application. It is requested that they be restored to consideration and allowed if amended Claim 3 is allowed, as allowance of Claims 7-11 is consistent with allowance of amended Claim 3.

We turn now to the rejections.

Claim 6 is rejected under 35 U.S.C. 112, first paragraph, on the basis that the breadth of the limitation "selective inhibitor of cyclooxygenase-2 directly inhibits the enzyme cyclooxygenase-2 and also inhibits the synthesis of cyclooxygenase-2 protein" is not enabled by the specification. The rejection relies on General Electric Company v. Wabash Appliance Corporation 37 U.S.P.Q. 466 (Sup. Ct. 1938) and University of California v. Eli Lilly, 43 U.S.P.Q. 2d 1398, 1406 (Fed. Cir. 1997). Reconsideration is requested.

The rejection under 35 U.S.C 112, first paragraph, is wrong firstly because General Electric is misapplied in the rejection. General Electric rather holds that for a predecessor statute R.S. § 888, 35 U.S.C. § 33, there is enablement for a functional limitation, i.e., General Electric is not inconsistent with Claim 6 being enabled here.

The rejection under 35 U.S.C. 112, first paragraph, is wrong secondly because University of California v. Eli Lilly is misapplied in the rejection. University of California holds that broad genus of cDNAs may be achieved analogous to enablement, by recitation of a plurality of species. In the undersigned's experience, the PTO allows generic coverage of a cDNA based on recitation of nucleotide sequences of two species. Here, four species are recited. See the application as filed at page 18. It is submitted that if University of California is pertinent at all here, i.e., is not limited to genera of genetic material, it supports a finding of enablement for Claim 6.

The rejection under 35 U.S.C. 112, first paragraph, is wrong thirdly because the rejection does not meet the burden that the PTO has for enablement rejections of providing evidence or reasoning as to why one skilled in the art would not be able to conceive of many more species meeting Claim 6, given Applicant's disclosure. See In re Dinh-Nguyen, 181 U.S.P.Q. 46, 47 (CCPA 1974); In re Bowen, 181 U.S.P.Q. 48 (CCPA 1974); In re Gardner, 177 U.S.P.Q. 396, 397 (CCPA 1973); and Ex parte Reese, 40 U.S.P.Q. 2d 1221 (Bd. App. 1996).

Consider the following statement from In re Hallman, 210 U.S.P.Q. 609, 611 (CCPA 1981): "It is well settled there is nothing intrinsically wrong in defining something by what it does rather than by what it is."

Withdrawal of the rejection under 35 U.S.C. 112, first paragraph, is requested.

We turn now to the rejection under 35 U.S.C. 102. Claims 1-5 are rejected under 35 U.S.C. 102(e) as being anticipated by Gregory et al. U.S. Patent No. 6,172,096. Reconsideration is requested. In respect to Claims 1 and 2, there is no anticipation because Gregory et al. fails to teach or disclose treating liver disease without administration of leukotriene B_4 receptor antagonist. So far as Claims 3-6 and 17 are concerned, Gregory is defective in failing to teach treatment of chronic viral hepatis B, chronic viral hepatitis C, alcoholic liver injury and nonalcoholic steatohepatis.

We turn now to the rejections under 35 U.S.C. 103(a).

Claims 1-6 are rejected under 35 U.S.C. 103(a) as being obvious over Gregory et al. U.S. Patent No. 6,172,096 in view of Talley et al. U.S. Patent No. 5,643,933. Reconsideration is requested. Consider firstly that cyclooxygenase inhibitors in the form of NSAIDs have received considerable attention in recent years in respect to the risk of hepatotoxicity and that the Arthritis

Advising Committee of the FDA concluded in 1982 that hepatotoxicity is a class characteristic of NSAIDs. See Zakim, D., et al. Hepatology A Textbook of Liver Disease, Volume II, Third edition, W. B. Saunders, Philadelphia (1996), pages 976 and 977, copy enclosed. Consider also that the combination of Gregory and Talley does not teach treatment of liver disorders without an administration of leukotriene B_4 receptor antagonist (Claims 1 and 2) or of chronic viral hepatitis B, chronic viral hepatitis C, alcoholic liver injury and nonalcoholic steatohepatitis (Claims 3-6 and 17) especially in view of the hepatotoxicity associated with some NSAIDs as described in Zakim et al., pages 976-977 attached. Talley et al. seems to be relied on only for disclosing the treating agent of Claim 6. Even if Talley did this, Claim 6 is patentable for the reasons recited above. However, Talley et al. does not disclose the treating agent of Claim 6. Note this is not a case of inherent functionality as the Office Action suggests. Note that cyclooxygenase-2 enzyme has two activities, i.e., cyclooxygenase activity and peroxidase activity. Conventional selective inhibitors of cyclooxygenase-2 suppress cyclooxygenase activity but not peroxidase activity. On the other hand, knocking out synthesis of the enzyme affects both activities. Moreover, suppression of synthesis of cyclooxygenase-2 enzyme changes protein-protein interactions which the science of proteomics associates with disease symptoms. Thus, inhibition of enzyme cyclooxygenase activity is different from and more limitive than inhibition of enzyme synthesis and both modes are not associated with conventional selective inhibitors of cyclooxygenase-2. Moreover, for the Office Action to suggest inherency, there must be some logical basis for the possibility. Here, that is missing. In any event, inherency and what is required for such, are not appropriate considerations for an obviousness rejection, and thus

reliance on that is misplaced here. The discovery of a new function can clearly be a basis for unobviousness, even if that were what is involved here.

Finally, Claims 1-6 are rejected as unpatentable over Talley, et al. U.S. 5,643,933 (further in view of Talley et al. 5,643,933? --same repeated twice). The Office Action takes the position that Talley et al. teaches treating inflammation associated disorders and that hepatitis (recited in Claim 1 and treated in Claim 1) is an inflammation associated disorder. Reconsideration is requested. It is submitted that amended Claims 1 and 3 and the claims dependent thereon are unobvious over Talley because it is not obvious from Talley that there would be a net benefit for the instant invention when a committee of the FDA has concluded that hepatoxicity is a "class characteristic" of NSAIDs which are non-selective inhibitors of cyclooxygenase-2.

Allowance is requested.

Respectfully submitted,

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Case CRF D-2165

January 7, 2002

VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS:

Claim 1 has been amended as follows:

1 (amended). A method of treating a patient with a liver disease comprising administering to said patient a cyclooxygenase-2 inhibiting amount of a selective inhibitor of cyclooxygenase-2 without administration of leukotriene B_4 receptor antagonist.

Claim 3 has been amended as follows:

3 (amended). [The method of Claim 2, wherein the inflammatory liver disorder is] A method of treating a patient with a liver disease selected from the group consisting of chronic viral hepatitis B, chronic viral hepatitis C, alcoholic liver injury [primary biliary cirrhosis, autoimmune hepatitis,] and nonalcoholic steatohepatitis[, and liver transplant rejection], comprising administering to said patient a cyclooxygenase-2 inhibiting amount of a selective inhibitor of cyclooxygenase-2.

Claims 12-16 have been canceled.

Claim 17 has been added as follows:

--17. The method of Claim 6 wherein the selective inhibitor of cyclooxygenase-2 contains phenyl group with two or more substituents selected from the group consisting of hydroxy and C_{1-4}-alkoxy on the phenyl group.--

HEPATOLOGY

A Textbook of Liver Disease

VOLUME II

THIRD EDITION

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are mild to moderate increases in serum aminotransferase activity and blood ammonia levels and, much less commonly, subclinical hyperbilirubinemia.[96-101] Jaundice is uncommon. Severe clinical hepatitis is rare, although nonfatal cases with hypoprothrombinemia and encephalopathy have been reported.[100, 102]

The histologic finding is a nonspecific focal hepatitis.[99] Massive or submassive necrosis has not been established as a consequence of high-dose aspirin therapy, and there is typically no apparent increase in hepatocellular fat. The rare occurrence of acute encephalopathy and anicteric liver dysfunction[103] with microvesicular hepatic steatosis in children with salicylate intoxication[104] has suggested an overlap between a rare subset of salicylate hepatotoxicity and Reye's syndrome. Although the usual form of hepatotoxicity associated with high-dose salicylate therapy differs both clinically and histopathologically from Reye's syndrome, a strong association has been established between the therapeutic use of aspirin in children and the development of Reye's syndrome.[33] In experimental animals, salicylic acid inhibits the mitochondrial beta-oxidation of long-chain fatty acids.[105] The existence of inborn errors of metabolic enzymes of mitochondrial beta-oxidation in approximately one third of children who develop Reye's syndrome[33] may confer a particular susceptibility upon these children for the development of a unique form of hepatic metabolic insult from aspirin.

Aspirin hepatotoxicity is rapidly and completely reversed when the drug is discontinued. The dose dependency of the lesion is well established. The injury usually is associated with serum salicylate levels in excess of 25 mg/dL (a daily dose of about 3 to 5 g in adults), but about 2 per cent of instances of toxicity occurred at levels of less than 10 mg/dL.[99] Patients with chronic rheumatic diseases have been thought to be at greater risk for developing hepatotoxicity with aspirin,[100] but the frequency of increased serum aminotransferase activity is similar in these patients and in children treated with aspirin for acute rheumatic fever—about 50 per cent.[101] It has been suggested that reduced serum albumin concentrations, by increasing the unbound fraction of aspirin, might predispose to injury.[4]

OTHER SALICYLATES

Sulfasalazine. This compound is split into its component sulfapyridine and 5-aminosalicylate moieties in the colon. The sulfapyridine is mostly absorbed and is believed to be responsible for hepatotoxic reactions. Liver injury has been reported in young patients treated for inflammatory bowel disease and rheumatoid arthritis. Typically, a florid hypersensitivity reaction with accompanying rash, lymphadenopathy, leukocytosis, eosinophilia, hypocomplementemia, and circulating immune complexes begins within 3 weeks of starting the drug.[106, 107] Fulminant hepatic failure has occurred in spite of discontinuation of the drug, and resolution has been aided in anecdotal cases by high-dose intravenous corticosteroids.[106] The clinical picture of sulfasalazine hepatotoxicity is typical of sulfa drug hypersensitivity; and the newer agents used to treat inflammatory bowel disease that contain only 5-aminosalicylate and its derivatives are expected to produce far fewer adverse effects. Nonetheless, the 5-aminosalicylate moiety is not entirely exonerated as evidenced by the rare occurrence of a hypersensitivity hepatitis to *mesalazine* after a previous episode of sulfasalazine-induced hepatitis.[108]

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

The risk of hepatotoxicity from NSAIDs has received considerable attention in recent years.[4, 109, 110] The Arthritis Advising Committee of the Food and Drug Administration (FDA) concluded in 1982 that hepatotoxicity is a "class characteristic" of this group of drugs.[4] This unfortunately belies the fact that individual NSAIDs differ widely in their propensity to produce liver damage. Certain agents, including benoxaprofen and ibufenac, produced severe and often fatal hepatotoxicity with such frequency that they were withdrawn soon after introduction.[4] Others, such as meclofenamic acid and mefanamic acid, appear relatively free of hepatotoxic potential.[109] A large retrospective cohort study in Canada estimated the actual increased risk of hepatotoxicity from taking NSAIDs to be quite small, about 5 per 100,000 person-years.[111] Risk factors for the development of liver damage from NSAIDs include advanced age, renal insufficiency, multiple drug use, use of high doses, and concomitant alcohol use.[112] Of the currently available NSAIDs in the United States, diclofenac, sulindac, and phenylbutazone appear to carry the greatest risk of hepatotoxicity; piroxicam, ibuprofen, naproxen, and fenoprofen carry an intermediate risk.[109] The basis for hepatotoxicity from NSAIDs appears to be largely, but not entirely, idiosyncratic; and cross-sensitivity between different classes of NSAIDs may occur.[113]

Diclofenac. Fifteen per cent of patients treated with this benzene–acetic acid derivative display borderline (<1.5-fold) elevations in serum aminotransferases, whereas in 2 per cent, aminotransferase elevations exceed threefold normal.[109] Over 30 cases of hepatotoxicity have been attributed to diclofenac.[114-118] The duration of treatment before the onset of the illness has ranged from 1 week to 14 months. The type of injury has been predominantly hepatocellular, and features of hypersensitivity have been rare. Symptoms at the time of onset have included jaundice, nausea, and abdominal pain. Liver histology has variably shown a nonspecific acute hepatitis and zonal and massive necrosis.[118] Although most patients have recovered fully after withdrawal of the drug, fatalities from massive hepatic necrosis have occurred.[114] In addition, at least four patients have developed a syndrome not unlike autoimmune chronic hepatitis with positive antinuclear antibodies.[115, 119] Monitoring of serum aminotransferases is recommended every 3 to 6 months in patients being treated for prolonged periods with diclofenac with discontinuation of the drug if levels exceed threefold normal.

Sulindac. This indole–acetic acid derivative has been implicated in a number of individual reports of hepatotoxicity as well as in numerous reports to the FDA.[4] The clinical presentation is usually painless jaundice with evidence of a mild hepatitis with variable cholestatic features. Fever

(4)

and rash may be present. Recovery upon withdrawal of the drug may take several months.[120]

Piroxicam. The oxicam NSAIDs appear to have a modest potential for inducing hepatotoxicity, which is nevertheless important in view of the extensive use of piroxicam. The toxicity of this drug has manifested primarily as cholestatic hepatitis with features of hypersensitivity in elderly patients. At least two fatalities have been documented.[4, 121, 122]

Benoxaprofen. This drug was withdrawn soon after its introduction following 60 deaths from hepatorenal toxicity in elderly patients. The liver disease was mainly cholestatic with characteristic laminated concretions filling bile ductules on histology. Deaths may have resulted from toxic blood levels of the drug, elimination of which was substantially impaired by the combination of cholestasis and renal failure.[4, 109]

Phenylbutazone. Phenylbutazone has been associated with overt hepatic injury in about 0.25 per cent of patients. The onset of the reaction usually occurs in the first 6 weeks of treatment but may be delayed by as much as 1 year.[123]

The reaction may take several forms. Most often the illness resembles viral hepatitis in its presentation, and in about 50 per cent of patients there may be antecedent fever, rash, or arthralgia. Clinical and laboratory findings are consistent with an acute hepatitis, and liver biopsy may show a typical viral hepatitis–like picture, submassive or massive necrosis. Fatal hepatitis has occurred. Less commonly, the appearance of the disorder may be cholestatic with little clinical or histologic evidence of significant hepatocellular necrosis. Noncaseating granulomas may accompany the hepatic reaction, usually in association with minor hepatocellular injury. Histologic changes indistinguishable from those seen in primary biliary cirrhosis have been observed in one patient.[123]

The mechanism of the injury is unknown. Although certain clinical features suggest hypersensitivity to the drug, phenylbutazone is hepatotoxic in laboratory animals,[2] and overdoses with this drug have produced acute hepatic necrosis in humans.[123]

OTHER ANTIRHEUMATIC DRUGS

Allopurinol. Allopurinol may lead to liver cell injury, usually within a period of 5 weeks.[124, 125] Fever, skin rash, and eosinophilia are not uncommon, with moderate aminotransferase elevation and jaundice. Occasionally, there is a severe systemic reaction with vaculitis and renal failure.[126] Diuretic use and renal impairment may predispose to the development of allopurinol hepatotoxicity.[124] The pathologic findings include centrolobular necrosis as well as features indistinguishable from viral hepatitis, with eosinophils being prominent. Massive hepatic necrosis also has been described,[127] but the disorder is rarely fatal. Granulomas, which may show a fibrin-ring structure similar to those seen in Q-fever,[128] are reported in about 50 per cent of liver biopsies and have been described in bone marrow.[125]

Gold. Gold salts used in the treatment of rheumatoid arthritis occasionally cause a relatively noninflammatory, cholestatic form of liver injury.[129, 130] The onset usually has occurred within a few weeks after the start of the course of drug administration, and has responded well to cessation of treatment. The incidence and mechanism of toxicity are unknown. A rare form of dose-dependent hepatotoxicity may occur late in the course of gold therapy. Hepatocellular necrosis is the predominant histologic finding and characteristic dense, needle-shaped lysosomal inclusions (aurosomes) are seen on electron microscopy.[131]

OPIATE ANALGESICS

Dextropropoxyphene. This widely used opiate analgesic has been believed to be hepatotoxic in rare instances. However, a recent report described nine cases—almost half of the reported cases—of dextropropoxyphene-associated cholestatic hepatitis presenting to a single center within an 18-month period.[132] This remarkable epidemiologic phenomenon suggests that hepatotoxicity with this drug may have been poorly recognized and underreported in the past. Affected individuals have been men and women aged 30 to 65 (75%). The onset of symptoms occurred within 2 to 90 days of starting therapy, and often suggested acute cholecystitis with upper abdominal pain, jaundice, and malaise. Laboratory tests revealed a predominantly cholestatic pattern. Liver histology showed cholestasis with features of bile duct injury, periductal fibrosis, and inflammation and edema—features of large duct obstruction. The mechanism of injury is unknown, but the absence of immune features suggests metabolic idiosyncrasy. Complete recovery within 3 months of stopping therapy has been the rule.

SKELETAL MUSCLE RELAXING DRUGS

Dantrolene. This is an antispasmodic agent related to phenytoin. In a prospective study, prolonged (more than 2 months) use of the drug was associated with a 1.8 per cent incidence of liver function abnormalities; of the 19 affected patients, 6 were jaundiced and 3 died.[133] Additional experience indicates that asymptomatic aminotransferase elevation is common, and that significant liver injury caused by dantrolene occurs only after a month or more of use and is more likely to occur among patients 30 years old or older or when doses exceed 300 mg/day.[133, 134] Marked hyperbilirubinemia (>10 mg/dL) carries a poor prognosis. Clinically, the disease resembles acute or chronic viral hepatitis, and histologically it may be associated with bridging or submassive necrosis or progression to cirrhosis. A very high case fatality rate (22 to 28 per cent) has been reported.[133, 134] It has been recommended that liver tests be monitored in all patients treated with this agent.[133, 134] Experimental studies have shown that dantrolene is converted to an electrophilic metabolite by cytochrome P450 with covalent binding to hepatic proteins and inhibition of cytochrome P450. This sequence of events, however, has not been shown to result in hepatic necrosis.

Chlorzoxazone. This centrally acting muscle relaxant has been implicated in several instances of acute hepatic